

## **REMARKS**

Reconsideration of the application, as amended, is respectfully requested. The Applicants wish to draw the Examiner's attention to the applicants' related co-pending applications and issued patents (see Appendix A) directed to nanoparticles and methods of preparation and use thereof. Office actions have already issued on many of the listed cases.

### **Status of the claims**

Claims 3-19, 32-34 and 36 were pending in this application. These claims were cancelled without prejudice or disclaimer and replaced with new claims 37-72. Support for the new claims can be found in the application as originally filed. See original claims and the specification at page 11, line 22-30; page 12, line 17-28; and page 13, lines 7-14. Accordingly, no new matter has been introduced into this application as a result of the present amendment.

### **Priority Claim**

Turning now to the Office action, the Examiner asserted that the priority dates for claims 6-9 and 32-34 (now claims 42-45 and 69-71) can only extend to the filing date of the application, specifically December 28, 2001. Applicants respectfully traverse this assertion. The provisional application 60/293,861, filed May 25, 2001 discloses and recognizes the broad utility of the claimed core/shell nanoparticle conjugates. This utility includes the tailorability of the physical properties of the core/shell nanoparticles through the use of a variety of biomolecules and nanoparticle cores that can be chosen depending on the particular desired properties, as disclosed, for example, on the last page of the specification. Thus, Applicants respectfully assert that the entirety of the claims are entitled to the filing date (May 25, 2001) of the provisional application.

### **Claim interpretation**

The term nanoparticles have been defined in the Applicant's prior applications which have been incorporated by reference in their entirety. See the specification at page 8, line 31 to page 9, line 5. For instance, U.S.S.N. 09/760,500 (now Applicant's U.S. Patent no. 6,767,702), recites suitable nanoparticles having a size ranging from 5 to about

150 nm (mean diameter) See, for instance, the original claims and the specification at pages 8, line 31 to page 9, line 5. See also the specification at page 10, line 29; page 11, line 2; ; page 12, line 28; and page 13, line 18.

### **Claim Rejection under 35 USC § 102**

Claims 3-5, 7, and 10-16 (now claims 37, 38, 40, 42, 45, and 55-60) stand rejected under 35 U.S.C. § 102(e), alleged to be anticipated by Abbott et al. (U.S. Patent 6,277,489)(“Abbott”). The Examiner alleged that the present invention is old because Abbott allegedly taught a multilayered material comprising a particulate substrate, a metal film layered onto the substrate, and a recognition moiety attached to the metal layer. Further the particulate substrate is alleged to be any size. On this basis, the Examiner believes that Abbott anticipates the claimed invention. The Applicants respectfully traverse the rejection.

As a general rule, for prior art to anticipate under section 102, every element of the claimed invention must be identically disclosed in a single reference. Coming Glass Works v. Sumitomo Electric, 9 U.S.P.Q.2d 1962, 1965 (Fed. Cir. 1989). The exclusion of a claimed element, no matter how insubstantial or obvious, from a reference is enough to negate anticipation. Connell v. Sears, Roebuck & Co., 220 U.S.P.Q 193, 1098 (Fed. Cir. 1983). Applicants respectfully submit that none of the references cited against the pending claims can be applied to support an anticipation rejection of the claims under 35 U.S.C. sections 102 (b) and (e).

Abbott fails to teach the elements of the instant invention as presently claimed. While Abbott relates to a multilayered material of particulate substrate, a metal film layered onto the substrate, and a recognition moiety e.g., biomolecules, attached to the metal layer, a disclosure of a substrate, metal film and recognition moiety is not a disclosure of the present invention as claimed. Abbott merely deals with conventional coating methods as discussed in col. 11, lines 51-55; col. 37, lines 24-32; col. 55, lines 59-66. The present invention, as claimed, is drawn to a core/shell nanoparticle oligonucleotide conjugate comprising an metal-containing core; a non-alloying gold shell surrounding the nanoparticle core; and oligonucleotides attached to the gold shell, wherein “the core of the core/shell nanoparticle does not exhibit a red shifting and broadening of

the plasmon resonance band relative to a core surrounded by an alloyed gold shell”, a method of preparation, and method of use.

First, Abbott does not disclose or suggest anywhere a “non-alloying” gold shell metal coating as presently claimed. Secondly, Abbott does not disclose or suggest “the non-alloying gold shell is generated on a surface of the core by simultaneous addition of a solution comprising a gold salt and a solution comprising a reducing agent to a solution containing the metal core” as presently claimed. Accordingly, Abbott cannot be said to anticipate the presently claimed invention. Withdrawal of the section 102(b) reference is in order and is respectfully requested.

### **Claim Rejection under 35 USC § 103**

Claims 8-9 and 32-34 (now claims 44, 45, and 69-71) stand rejected under 35 U.S.C. § 103(a), alleged as unpatentable over Abbott (cited above) as applied to claims 3 and 7, in view of Mirkin et al. (US 6,361,944)(“Mirkin”). More specifically, Abbott is re-alleged as above while Mirkin is alleged to teach nanoparticle-oligonucleotide conjugates used in detection of nucleic acids, wherein the nanoparticles are magnetic, including cores of Fe<sub>3</sub>O<sub>4</sub> with a silica shell, conjugated to oligonucleotides. Mirkin is further alleged to teach nanoparticle-oligonucleotide conjugates in hybridization methods, including methods for detection on a surface. The Examiner asserts that it would be obvious to an ordinary skilled artisan to use the magnetic core of Mirkin in the particles of Abbott, motivated by the desire for easy separation of magnetic particles having hybridized targets from a test solution. Applicants respectfully traverse the rejection.

The Federal Circuit reiterated the manner in which obviousness rejections are to be reviewed. Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, "a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991), citing *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir.

1988). Applicants respectfully submit that the combination of Abbott and Mirkin does not teach or suggest the Applicants' invention as presently claimed.

As described in the specification of the instant application, the present invention relates to a method for preparing core/shell nanoparticle conjugates having a non-alloying gold shell, conjugates prepared by the method, and methods for using the conjugates. Conjugates prepared by the present invention having such non-alloying gold shells surprisingly and unexpectedly retain the physical and/or optical properties of the core with no observed physical or optical competing effects from the non-alloying gold shell and further maintain the versatile surface chemistry of gold. The preservation of the optical properties of the core through the formation of a non-alloying gold shell allows the conjugates of the present invention to be used in alternative analyte detection systems, e.g, colorimetric detection systems.

Prior to the instant invention, conventional methods for preparing core/shell nanoparticles having gold shells resulted in core/shell nanoparticles that exhibit an undesirable change in optical properties such as broadening and shifting of the plasmon resonance characteristics. This undesirable optical change was due to the formation of gold alloys between the gold shell and the core material. For instance, a number of labs have reported on procedures for preparing gold coated silver nanoparticles. Nanoparticles produced by such conventional procedures were found to exhibit a characteristic red shifting and broadening of the plasmon resonance for silver due to the formation of a gold/silver alloy. In contrast, the core/shell silver/gold nanoparticles prepared by the method of the present invention are not alloyed and further retain the optical properties of the silver core with no red shifting of the silver plasmon band. The nanoparticles of the invention can be further functionalized with molecules for analyte detection by taking advantage of the surface chemistry of gold. See page 4, line 32 to page 5, line 8 and page 13, line 31 to page 14, line 17 of the specification.

Contrary to the Examiner's position, Abbott is completely silent with respect to any non-alloying gold core/shell nanoparticle. Furthermore, Abbott is completely silent with respect to the problem of preparing core/shell nanoparticles that retain the physical/optical properties of the core. Nor does Abbott provide any solution to this problem. Mirkin adds nothing to Abbott that could render the presently claimed invention obvious.

The failure of Abbott, the primary reference, to teach or suggest the claimed subject matter is discussed above. Even assuming, *arguendo*, that Mirkin does teach, as alleged, nanoparticle-oligonucleotide conjugates used in detection of nucleic acids, wherein the nanoparticles are magnetic, including cores of Fe<sub>3</sub>O<sub>4</sub> with a silica shell, conjugated to oligonucleotides, and such conjugates in hybridization methods, including methods for detection on a surface, such a disclosure does not cure the deficiencies of Abbott. Moreover, even if the alleged cores of Mirkin are combined with the disclosure of Abbott as the Examiner would have it, one of skill would not arrive to the claimed nanoparticle core/shell oligonucleotide conjugates, as claimed. Accordingly, Applicants respectfully submit that withdrawal of the rejection of the claims under 35 U.S.C. § 103(a) based on the combination of Abbott with Mirkin is in order and is respectfully requested..

**Provisional Double Patenting rejection (same invention)**

The Examiner rejected claims 3-10 (now claims 37, 38, and 40-46) of the present application for double patenting in view of claims 2-8 of co-pending application serial no. 10/153,483 and claims 3-10 of co-pending application serial no. 10/397,579. The Applicants request that the Examiner hold this rejection in abeyance until the claims in this application or either of the co-pending application have been found to be allowable.

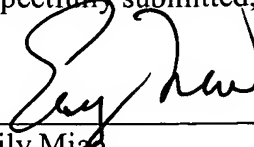
**Provisional Double Patenting rejection (obviousness-type)**

The Examiner rejected claims 32-34 (now claims 69-71) of the present application for double patenting in view of claims 35-37 of co-pending application serial no. 10/153,483 and claims 32-34 of co-pending application serial no. 10/397,579. The Applicants request that the Examiner hold this rejection in abeyance until the claims in this application or either of the co-pending application have been found to be allowable.

**Conclusion**

In light of the above arguments, the Examiner is respectfully requested to reconsider the application as claimed. If the Examiner believes that a telephonic or personal interview would expedite prosecution of the application, she is invited to contact the undersigned at (312) 913-0001.

Respectfully submitted,



---

Emily Miao

Registration No. 35,285

Date: September 27, 2004

McDonnell Boehnen Hulbert & Berghoff LLP  
300 South Wacker Drive, Suite 3200  
Chicago, IL 60606  
Tel. No. 312-913-0001  
Fax No. 312-913-0002



September 27, 2004

Page 1 of 7

**APPENDIX A**

| <b>ATTY<br/>Case No.</b> | <b>Serial No./<br/>Filing Date</b>     | <b>Inventors/Title</b>   | <b>Status</b>   |
|--------------------------|--|--|---|
| <b>00-653-G</b>          | U.S. 10/794,741<br>Filed 3/5/04        | Mirkin, Letsinger,<br>Mucic, Storhoff,<br>Elghanian, Taton,<br>Garamella, Li, Park/<br>NANOPARTICLES<br>HAVING<br>OLIGONUCLEOTI<br>DES ATTACHED<br>THERETO AND<br>USES THEREFORE | ALLOWED   |
| <b>00-713-B1</b>         | 09/923,625<br>Filed 8/7/01             | Mirkin, Letsinger,<br>Mucic, Storhoff,<br>Elghanian/<br>NANOPARTICLES<br>HAVING<br>OLIGONUCLEOTI<br>DES ATTACHED<br>THERETO AND<br>USES THEREFOR                                 | ALLOWED   |
| <b>00-713-C</b>          | 09/344,667, filed<br>6/25/99           | Mirkin, Letsinger,<br>Mucic, Storhoff,<br>Elghanian/<br>NANOPARTICLES<br>HAVING<br>OLIGONUCLEOTI<br>DES ATTACHED<br>THERETO AND<br>USES THEREFORE                                | U.S. Patent No.<br>6,361,944, issued<br>3/26/02       |
| <b>00-713-I</b>          | U.S.S.N<br>09/603,830<br>Filed 6/26/00 | Mirkin, Letsinger,<br>Mucic, Storhoff,<br>Elghanian, Taton;<br>NANOPARTICLES<br>HAVING<br>OLIGONUCLEOTI<br>DES ATTACHED<br>THERETO AND<br>USES THEREFOR                          | U.S. Patent No.<br>6,506,564, issued<br>1/14/03       |
| <b>00-713-I-1</b>        | 09/961,949<br>9/20/01                  | Mirkin, Letsinger,<br>Mucic, Storhoff,<br>Elghanian, Taton;  | U.S. Patent No.<br>6,582,921, issued<br>June 24, 2003 |



September 27, 2004

Page 2 of 7

| ATTY<br>Case No. | Serial No./<br>Filing Date | Inventors/Title   | Status   |
|------------------|----------------------------|---|--|
|                  |                            | NANOPARTICLES<br>HAVING<br>OLIGONUCLEOTI<br>DES ATTACHED<br>THERE TO AND<br>USES THEREFOR |  |
| 00-713-I-2       | 09/957,318<br>9/20/01      | See 00-713-I-1  | U.S. Patent No.<br>6,759,199, issued<br>7/6/04           |
| 00-713-I-3       | 09/957,313<br>9/20/01      | See 00-713-I-1  | U.S. Patent No.<br>6,645,721, issued<br>11/11/03         |
| 00-713-I-4       | 09/966,491<br>9/28/01      | See 00-713-I-1  | U.S. Patent No.<br>6,610,491, issued<br>August 26, 2003  |
| 00-713-I-5       | 09/966,312<br>9/28/01      | See 00-713-I-1  | U.S. Patent No.<br>6,673,548, issued<br>January 6, 2004  |
| 00-713-I-6       | 09/967,409<br>9/28/01      | See 00-713-I-1  | U.S. Patent No.<br>6,740,491, issued<br>May 24, 2004     |
| 00-713-I-7       | 09/974,500<br>10/10/01     | See 00-713-I-1  | U.S. Patent No.<br>6,709,825, issued<br>March 23, 2004   |
| 00-713-I-8       | 09/974,007<br>10/10/01     | See 00-713-I-1  | PENDING  |
| 00-713-I-9       | 09/973,638<br>10/10/01     | See 00-713-I-1  | ALLOWED  |
| 00-713-I-10      | 09/973,788<br>10/10/01     | See 00-713-I-1  | U.S. Patent No.<br>6,720,411, issued<br>April 13, 2004   |
| 00-713-I-11      | 09/975,062<br>10/11/01     | See 00-713-I-1  | U.S. Patent No.<br>6,677,122, issued<br>January 13, 2004 |
| 00-713-I-12      | 09/975,376<br>10/11/01     | See 00-713-I-1  | PENDING  |
| 00-713-I-13      | 09/975,384<br>10/11/01     | See 00-713-I-1  | PENDING  |





September 27, 2004

Page 3 of 7

| ATTY<br>Case No. | Serial No./<br>Filing Date               | Inventors/Title                                      | Status  |
|------------------|--|--|---|
| 00-713-I-14      | 09/975,498<br>10/11/01                   | See 00-713-I-1                                       | ALLOWED   |
| 00-713-I-15      | 09/975,059<br>11/11/01                   | See 00-713-I-1                                       | ALLOWED   |
| 00-713-I-16      | 09/976,601<br>10/12/01                   | See 00-713-I-1                                       | PENDING   |
| 00-713-I-17      | 09/976,968<br>10/12/01                   | See 00-713-I-1                                       | ALLOWED   |
| 00-713-I-18      | 09/976,971<br>10/12/01                   | See 00-713-I-1                                       | U.S. Patent No.<br>6,682,895, issued<br>1/27/04         |
| 00-713-I-19      | 09/976,863<br>10/12/01                   | See 00-713-I-1                                       | PENDING   |
| 00-713-I-20      | 09/976,577<br>10/12/01                   | See 00-713-I-1                                       | U.S. Patent No.<br>6,720,147, issued<br>April 13, 2004  |
| 00-713-I-21      | 09/976,618<br>10/12/01                   | See 00-713-I-1                                       | ALLOWED   |
| 00-713-I-22      | 09/981,344<br>10/15/01                   | See 00-713-I-1                                       | U.S. Patent No.<br>6,777,186, issued<br>August 17, 2004 |
| 00-713-I-23      | 09/976,900<br>10/12/01                   | See 00-713-I-1                                       | ALLOWED   |
| 00-713-I-24      | 09/976,617<br>10/12/01                   | See 00-713-I-1                                       | U.S. Patent No.<br>6,730,269, filed<br>May 4, 2004      |
| 00-713-I-25      | 09/976,378<br>10/12/01                   | See 00-713-I-1                                       | PENDING   |
| 00-713-i-26      | 10/410,324<br>04/10/03                   | See 00-713-I-1                                       | PENDING   |
| 00-713-L         | U.S.S.N.<br>09/693,005<br>Filed 10/20/00 | Mirkin, Letsinger,<br>Mucic, Storhoff,<br>Elghanian/ | U.S. Patent No.<br>6,495,324, issued<br>12/17/02        |



September 27, 2004

Page 4 of 7

| ATTY<br>Case No. | Serial No./<br>Filing Date               | Inventors/Title  | Status  |
|------------------|--|--|---|
|                  |  | NANOPARTICLES<br>HAVING<br>OLIGONUCLEOTI<br>DES ATTACHED<br>THERETO AND<br>USES THEREFORE  |   |
| 00-713-M         | U.S.S.N.<br>09/693,352<br>Filed 10/20/00 | Mirkin, Letsinger,<br>Mucic, Storhoff,<br>Elghanian/<br>NANOPARTICLES<br>HAVING<br>OLIGONUCLEOTI<br>DES ATTACHED<br>THERETO AND<br>USES THEREFORE  | U.S. Patent No.<br>6,417,340, issued<br>7/9/02        |
| 00-714-G         | U.S. 09/830,620<br>Filed 8/15/01         | Mirkin, Nguyen/<br>NANOPARTICLES<br>WITH POLYMER<br>SHELLS   | PENDING   |
| 00-715-A         | U.S. 09/760,500<br>Filed 1/12/01         | Mirkin, Letsinger,<br>Mucic, Storhoff,<br>Elghanian, Taton;<br>Garamella, Li/<br>METHOD OF<br>ATTACHING<br>OLIGONUCLEOTI<br>DES TO<br>NANOPARTICLES<br>AND PRODUCTS<br>PRODUCED<br>THEREBY | U.S. Patent No.<br>6,767,702, issued<br>July 27, 2004 |
| 00-715-B         | U.S. 10/716,829<br>Filed 11/18/03        | Mirkin, Letsinger,<br>Mucic, Storhoff,<br>Elghanian, Taton;<br>Garamella, Li/<br>METHOD OF<br>ATTACHING<br>OLIGONUCLEOTI<br>DES TO<br>NANOPARTICLES<br>AND PRODUCTS<br>PRODUCED<br>THEREBY | Pending   |
| 00-1085-A        | U.S.S.N.                                 | Mirkin, Letsinger,   | U.S. Patent No.                                       |



September 27, 2004

Page 5 of 7

| ATTY<br>Case No. | Serial No./<br>Filing Date               | Inventors/Title  | Status  |
|------------------|--|--|---|
|                  | 09/820,279<br>Filed 3/28/01              | etc./ METHOD AND<br>MATERIALS FOR<br>ASSAYING<br>BIOLOGICAL<br>MATERIALS   | 6,750,016, issued<br>June 15, 2004            |
| 00-1085-G        | U.S.S.N.<br>10/640,618<br>Filed 8/13/03  | Mirkin, Letsinger,<br>etc./ METHOD AND<br>MATERIALS FOR<br>ASSAYING<br>BIOLOGICAL<br>MATERIALS   | Pending                                       |
| 00-1086-A        | U.S. 09/903,461<br>Filed 7/11/01         | Letsinger, Garimella/<br>METHOD OF<br>DETECTION BY<br>ENHANCEMENT<br>OF SILVER<br>STAINING   | U.S. Patent No.<br>6,602,669,<br>Filed 8/5/03 |
| 00-1272-C        | U.S.S.N.<br>10/008,978<br>Filed 12/7/01  | Mirkin, Letsinger,<br>Mucic, Storhoff,<br>Elghanian, Taton,<br>Garimella, Li, Park,<br>Lu/<br>NANOPARTICLES<br>HAVING<br>OLIGONUCLEOTI<br>DES ATTACHED<br>THERE TO AND<br>USES THEREOF | ALLOWED                                       |
| 01-565-A         | USSN 10/125,194<br>Filed 4/18/02         | Mirkin, Nguyen,<br>Watson, Park/<br>OLIGONUCLEOTI<br>DE-MODIFIED<br>ROMP POLYMERS<br>AND CO-<br>POLYMERS   | PENDING                                       |
| 01-599-A         | U.S.S.N.<br>10/291,291<br>Filed 11/08/02 | Storhoff/NOVEL<br>THIOL-BASED<br>METHOD FOR<br>ATTACHING<br>OLIGONUCLEOTI<br>DES TO<br>NANOPARTICLES   | PENDING                                       |
| 01-661-A         | U.S.S.N.<br>10/034,451                   | Mirkin, Cao, Jin/<br>DNA-MODIFIED  | PENDING                                       |



September 27, 2004

Page 6 of 7

| ATTY<br>Case No. | Serial No./<br>Filing Date               | Inventors/Title  | Status  |
|------------------|--|--|---------|
|                  | Filed 12/28/01                           | CORE-SHELL<br>AG/AU<br>NANOCRYSTALS  |         |
| 01-661-C         | U.S.S.N.<br>10/153,483<br>Filed 5/22/02  | Mirkin, Cao, Jin/<br>DNA-MODIFIED<br>CORE-SHELL<br>AG/AU<br>NANOCRYSTALS   | PENDING |
| 01-661-E         | U.S.S.N.<br>10/397,579<br>3/26/03        | Mirkin, Cao, Jin/<br>DNA-MODIFIED<br>CORE-SHELL<br>AG/AU<br>NANOCRYSTALS   | PENDING |
| 01-1565-A        | U.S.S.N.<br>10/266,983<br>Filed 10/08/02 | Park, Taton,<br>Mirkin/ARRAY-<br>BASED<br>ELECTRICAL<br>DETECTION OF<br>DNA USING<br>NANOPARTICLE<br>PROBES                            | PENDING |
| 01-1633-A        | U.S.S.N.<br>10/266,983<br>Filed 10/8/02  | Park, Taton,<br>Mirkin/NANOPARI<br>CLES HAVING<br>OLIGONUCLEOTI<br>DES ATTACHED<br>THERETO AND<br>USES THEREFOR                        | PENDING |
| 01-1705-A        | U.S.S.N.<br>10/108,211<br>Filed 3/27/02  | Nam, Park,<br>Mirkin/BIO-<br>BARCODES<br>BASED ON<br>OLIGONUCLEOTI<br>DE-MODIFIED<br>NANOPARTICLES                                     | PENDING |
| 02-338-B         | USSN 10/172,428<br>Filed 6/14/02         | Cao, Jin, Nam,<br>Mirkin/MULTI-<br>CHANNEL DETECTION<br>USING<br>NANOPARTICLE<br>PROBES WITH<br>RAMAN<br>SPECTROSCOPIC<br>FINGERPRINTS | PENDING |

| <b>ATTY<br/>Case No.</b> | <b>Serial No./<br/>Filing Date</b> | <b>Inventors/Title</b>   | <b>Status</b> |
|--------------------------|------------------------------------|--|---------------|
| <b>02-338-C</b>          | 10/431,341<br>5/7/03               | Cao, Jin, Nam,<br>Mirkin/MULTICHAN-<br>NEL DETECTION<br>USING<br>NANOPARTICLE<br>PROBES WITH<br>RAMAN<br>SPECTROSCOPIC<br>FINGERPRINTS                       | PENDING       |
| <b>02-1227-A</b>         | 10/735,357<br>Filed 12/12/03       | DIRECT SNP<br>DETECTION WITH<br>UNAMPLIFIED<br>NUCLEIC ACID<br>USING<br>NANOPARTICLE<br>PROBES   | PENDING       |
| <b>03-214-A</b>          | 10/789,831<br>Filed 2/27/04        | LABEL-FREE<br>GENE<br>EXPRESSION<br>PROFILING WITH<br>UNIVERSAL<br>NANOPARTICLE<br>PROBES IN<br>MICROARRAY<br>ASSAY FORMAT                                   | PENDING       |
| <b>03-466-C</b>          | 10/854,848<br>Filed 5/27/04        | METHOD FOR<br>DETECTING<br>ANALYTES<br>BASED ON<br>EVANESCENT<br>ILLUMINATION<br>AND SCATTER-<br>BASED<br>DETECTION OF<br>NANOPARTICLE<br>PROBE<br>COMPLEXES | PENDING       |
| <b>03-666-E</b>          | 10/877,750<br>Filed 6/25/04        | BIOBARCODE   | PENDING       |